DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(4), 503-534 (1994)

DEVELOPMENT OF A TRANS-MUCOSAL CONTROLLED-RELEASE DEVICE FOR SYSTEMIC DELIVERY OF ANTIANGINAL DRUGS PHARMACOKINETICS AND PHARMACODYNAMICS

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ABSTRACT

Oral mucosa is well-known to be one of the best routes for drug absorption. But very few R & D works have been initiated to investigate the feasibility of using this site to control drug delivery. A trans-mucosal controlled-release device, which is capable of achieving excellent absorption and controlled release of drugs, has been developed. The device is a tablet-shaped mucoadhesive system which is composed of two layers. The upper layer is a fast-release layer and

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the lower layer is a sustained-release layer, and designed to be applied between buccal and gingival mucosae. Both layers are formulated from synthetic polymers to control the release of drugs.

Isosorbide dinitrate(ISDN), a well-documented antianginal drug, is known to be susceptible to extensive presystemic elimination when taken orally. It was used as the candidate drug and the systemic bioavailability was studied in human and observed to be improved by as much as 5 fold when compared to a marketed oral sustained-release tablet ; On the other hand, much smaller amount of metabolites was formed. The plasma profile of ISDN has also been observed to be substantially prolonged (12 hrs as compared to less than 1 hr for sublingual tablet and spray product on the market). These observations have demonstrated that this device is capable of not only bypassing hepatic "first-pass" metabolism but also having a sustained-release property of prolonging the release of ISDN.

Clinical studies performed in the anginal patients for up to one year have demonstrated the therapeutic benefits of this device in achieving a substantial reduction in the frequency of anginal attacks.

This type of device was also applied to the systemic delivery of another antianginal drug, Nifedipine, by employing a formulation with longer sustained

drug release property. Again, the clinical results demonstrated that a prolonged duration of therapeutic plasma concentration has also been accomplished.

INTRODUCTION

Many R & D works have been conducted on development of controlled release drug delivery system for systemic delivery via oral or trans-dermal route of administration. However, these systems have their own drawbacks. For instance, the drug delivered by oral systems can not bypass hepatic "first-pass" metabolism, so, it is not suitable for drugs subjected to extensive hepatic "first-pass" metabolism. On the other hand, trans-dermal systems are difficult to promptly achieve a high systemic level of drugs, even though a steady level has also been attained without the hepatic "first-pass" metabolism.

The oral cavity (Figure 1) is covered by a lining of oral mucosa, which, histologically, can be viewed as a bilayer membrane consisting of a stratified squamous epithelium on the surface and a connective tissue underneath[1]. Similar to the skin, the oral mucosa acts, structurally and functionally, as the barrier to protect the underneath vital organs from the surroundings. At the submucosa level, a rete venosum is well

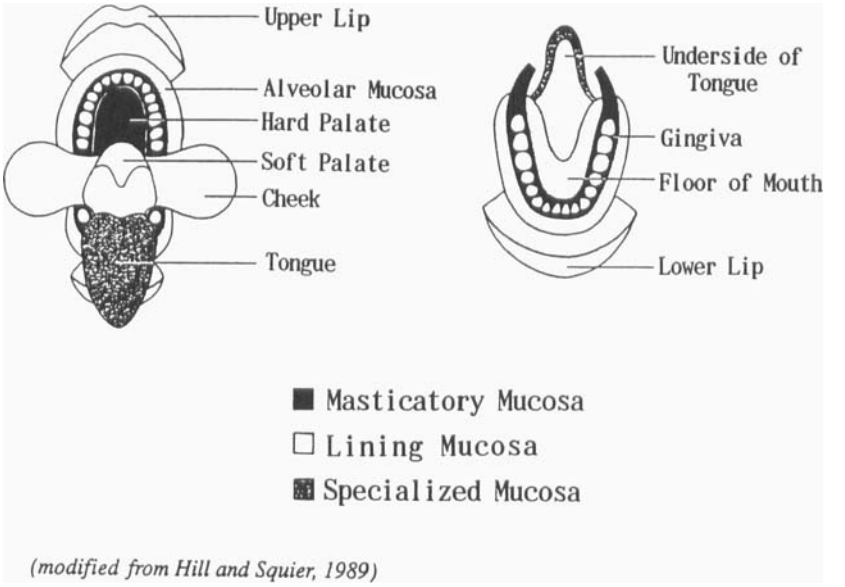

FIGURE 1
Histologic variation in the oral mucosa lining of human

developed, via which a substance absorbed by the oral mucosa enters at first the jugular vein and finally pours into the systemic circulation; thus the hepatic "first-pass" metabolism is avoided. From that reason, oral mucosa is well-known to be one of the best routes for drug administration. But, very few R & D works have been initiated to investigate the feasibility of using this site for rate-controlled drug delivery. There are several conventional oral dosage forms designed for application to the oral cavity, such as lorenzes, trouches, sublingual tablets and oral ointments. However, these conventional oral dosage forms give a disadvantageously abnormal feeling to patients

when they are kept in the oral cavity for long period of time, and hence, the patients occasionally wish to crunch or swallow them; therefore, they are not suitable for achieving the controlled release of drugs. The oral ointments are not crunched or swallowed, but they are difficult to control the dose. Among the oral mucosa, the gingival mucosa can be used as the platform for the holding of a drug delivery device designed for oral mucosa absorption. There have been some researches[2),3)] utilizing the gingiva for the application of controlled-release drug delivery system.

Organic nitrates have long been used for the treatment of angina pectoris. Among these organic nitrates, nitroglycerin (NTG) and isosorbide dinitrate (ISDN) are regarded as the therapeutic agents of first choice for the treatment of anginal attacks. ISDN has been demonstrated to exhibit a longer duration of antianginal activity than NTG. The manifestation of antianginal activity following the oral administration of ISDN has been well demonstrated[4)]. However, the duration of the clinical effect of oral ISDN is only 3-4 hrs, which is not sufficiently long to meet the therapeutic needs[5-7)]. Several oral sustained-release preparations of ISDN have been developed recently for clinical uses. However, ISDN, following oral administration, is extensively metabolized by the hepatic

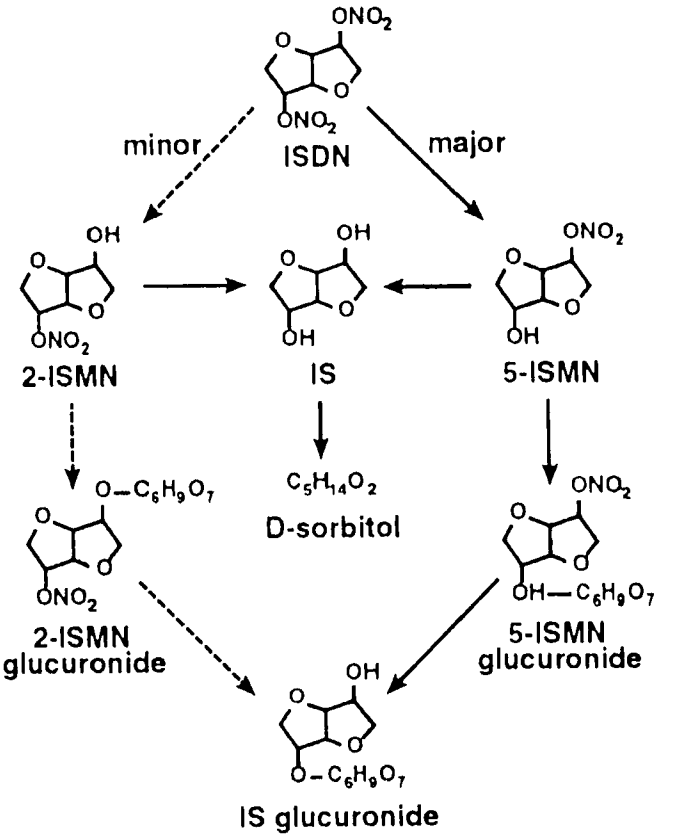

FIGURE 2
Metabolic pathway of Isosorbide dinitrate (ISDN) following oral administration and formation of major metabolites : 2-ISMN (isosorbide-2-mononitrate) , 5-ISMN (isosorbide-5-mononitrate) , IS (isosorbide)

"first-pass" metabolism to isosorbide-2-mononitrate (2-ISMN), isosorbide-5-mononitrate (5-ISMN) and other metabolites (Fig.2)[8),9)]. Thus, the systemic bioavailability of ISDN in humans has been reported to be as low as 22-29%[10-12)].

This presentation intends to provide an overview on the development of a novel trans-mucosal therapeutic

system (TmTs) designed to be applied to gingival mucosa to control the systemic delivery of drugs. ISDN was selected as a best drug for this system because its therapeutic efficacy is well established and has been known to be subjected to an extensive hepatic "first-pass" metabolism.

The characterization of the pharmaceutics and pharmacokinetics of the trans-mucosal controlled delivery of ISDN as well as the clinical performances are discussed in this presentation. Furthermore, the result of applying this system to another antianginal drug, Nifedipine, will also be reported.

DESIGN OF A TRANS-MUCOSAL THERAPEUTIC SYSTEM

Formulation development for the TmTs of ISDN was performed to design a system which is capable of achieving a good absorption of ISDN and long duration of its therapeutic effect, up to a duration of 12 hrs, by being applied on gingival mucosa. There were several hurdles to be overcome in the development, such as : the dosage form should have :(1) rapid and well adhesion to the gingival mucosa,(2) no irritation and sense of foreign material,(3) good absorption of ISDN,(4) rapid onset and long duration of therapeutic effect, and (5) easy manufacturing.

In order to satisfy both objectives of rapid onset and long duration of therapeutic effect, the system with a fast-release layer and a sustained-release layer was designed. Generally, it is not easy to attain a rapid and well adhesion to a wet surface as the gingival mucosa. Nagai et al[2] have found that a system formulated from a combination of hydroxypropylcellulose and polyacrylic acid has good adhesion property. Preformulation studies were initiated in our laboratory to search for good polymers that meet such criteria. The combination of a water-soluble polymer, such as polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol, alginic acid and malic acid-methylvinylether copolymer, and a water swellable polymer such as polyacrylic acid has shown good results. Among these polymers, the combination of polyvinylpyrrolidone and polyacrylic acid was identified to have the best adhesion property, and these were thus selected to be the mucoadhesive components in the sustained-release layer. For meeting the goal of easy manufacturing, simple compression process was employed to fabricate a tablet-shaped bi-layer TmTs (Figure 3). After various optimization studies, using adhesion test, dissolution study and animal pharmacokinetic evaluation, the final composition was determined. The sustained-release layer was shown to have the capacity of sustaining the

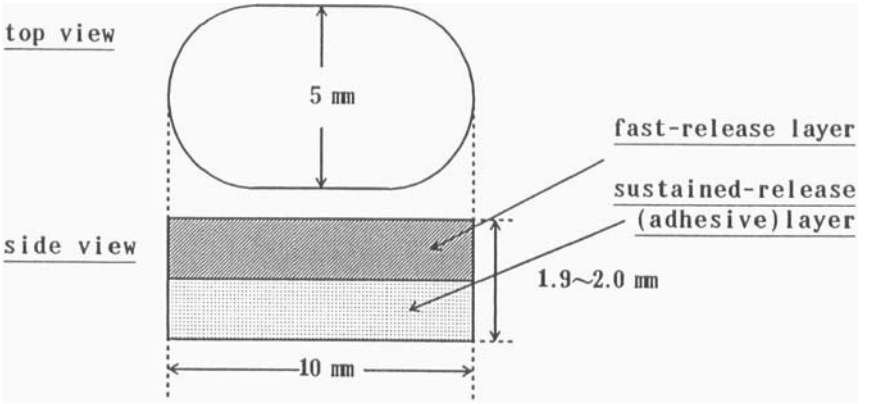

FIGURE 3
Physical structure and dimension of trans-mucosal therapeutic system (TmTs) formulation of isosorbide dinitrate

release of a drug by the effect of the gelling nature of both polymers. The fast-release layer is composed of 20% of ISDN, dispersed in the solid matrix of D-mannitol and polyvinylpyrrolidone of low molecular weight, while the sustained-release layer consists of 80% of ISDN in the polymer matrix of polyvinylpyrrolidone of high molecular weight and polyacrylic acid. The loading dose of ISDN in each layer was determined from the preferred plasma profile of ISDN. A small amount of polyvinylpyrrolidone of low molecular weight was added into the fast-release layer, since a too rapid disintegration of this layer was found to result in the loss of systemic bioavailability due to swallowing. Animal toxicological study, indicated that the system does not have any irritation to oral mucosa.

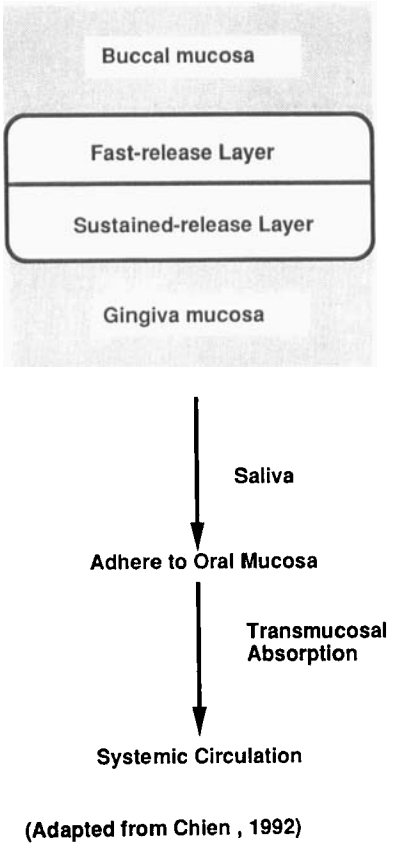

FIGURE 4
Mechanism of trans-mucosal absorption of drug delivered from TmTs applied to buccal and gingival mucosae

Thus, the newly-developed TmTs of ISDN could be expected to be a good controlled-release drug delivery system for gingival application, because it adheres to gingival mucosa easily and strongly, gives a desirable disintegration profile of the fast-release layer and the preferred gelation profile of the sustained-release layer, producing an initial rapid absorption and the subsequent continuous absorption of ISDN through oral mucosa by gradual dissolution in the saliva fluid

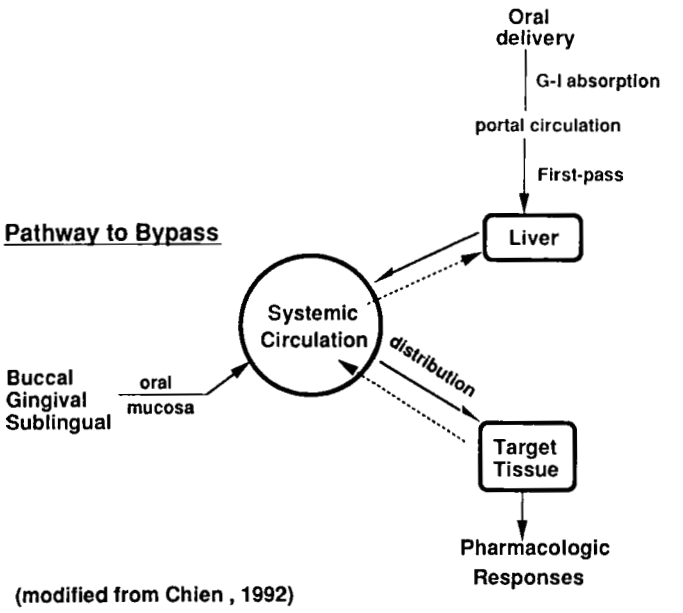

FIGURE 5
Hepato-gastrointestinal elimination of drugs following oral delivery and bypass through trans-mucosal absorption

(Figure 4). The ISDN absorbed permeates directly into systemic circulation and thus bypasses the hepatic "first-pass" metabolism (Figure 5).

DRUG RELEASE CHARACTERISTICS

Figure 6 shows the comparative release profiles of ISDN from the TmTs and from a conventional sublingual ISDN tablet (Nitrol®)[13]. The results indicate that the fast-release fraction (20%) of ISDN is released from the TmTs within 15min and the sustained-release fraction (80%) is released gradually and continuously

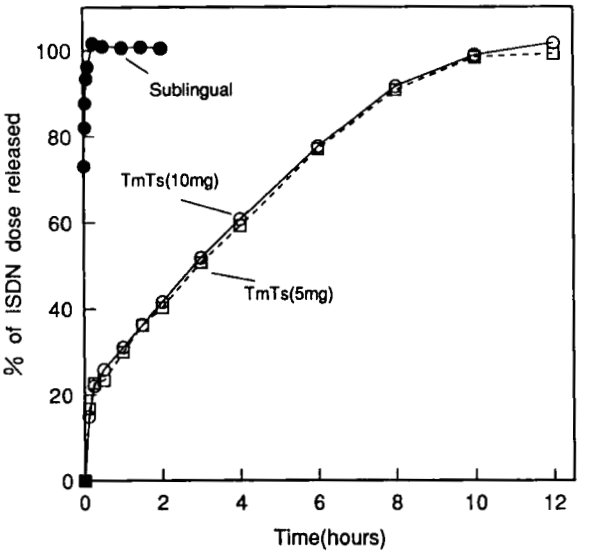

FIGURE 6
Comparative release profiles of ISDN from a sublingual tablet (Nitrol®, ● , 5mg of ISDN) and TmTs (□ , 5mg ; ○ , 10mg of ISDN) determined by dissolution studies (paddle method , Japanese Pharmacopeia , XII edition ; n=6)

over a period of 12 hrs. There is no difference in ISDN release profile between 5mg and 10mg dosage strengths. On the other hand, the release of ISDN from the conventional sublingual tablet is very rapid with the total dissolution of the tablet within approximately 15 min.

PHARMACOKINETICAL CHARACTERISTICS

Preclinical Studies in Beagle Dogs

In Figure 7, the plasma concentration profiles of ISDN from the TmTs as well as from its fast-release

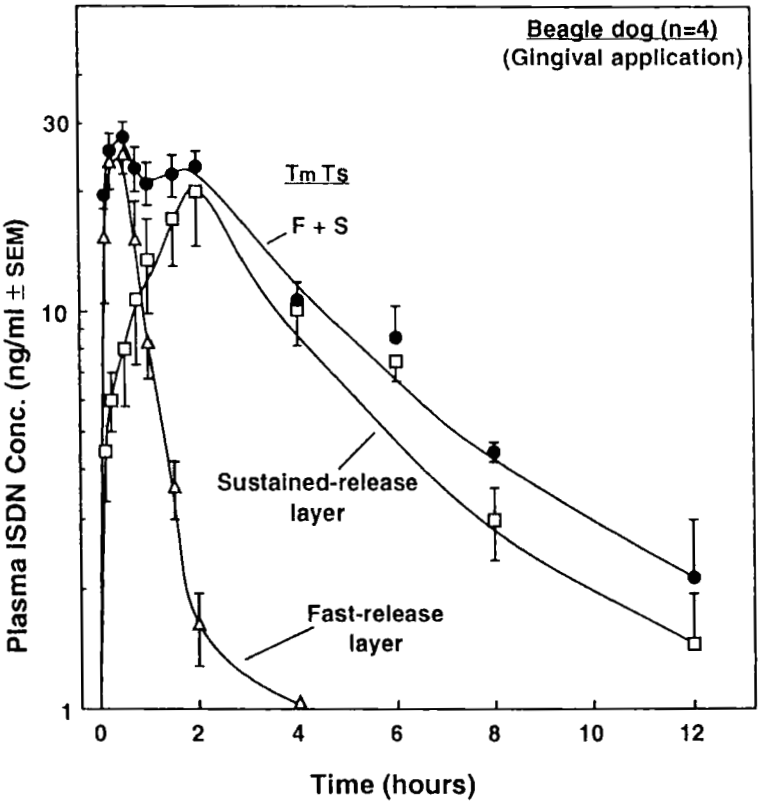

FIGURE 7

Effect of TmTs formulation on the pharmacokinetic profiles of ISDN in beagle dogs (n=4) Keys : (△) fast-release formulation , which contains 2mg of ISDN (only in the fast-release layer), (□) sustained-release formulation , which contains 8mg of ISDN (only in the sustained-release layer), (●) full formulation , which contains 2mg of ISDN in the fast-release layer (F) and 8mg of ISDN in the sustained-release layer (S)

and sustained-release layers are compared[13], which demonstrate that the plasma concentration profile is the consecutive transmucosal delivery of ISDN first from the fast-release fraction and then from the sustained-release fraction. Figure 8 shows the cumulative absorption profiles of ISDN from the TmTs in

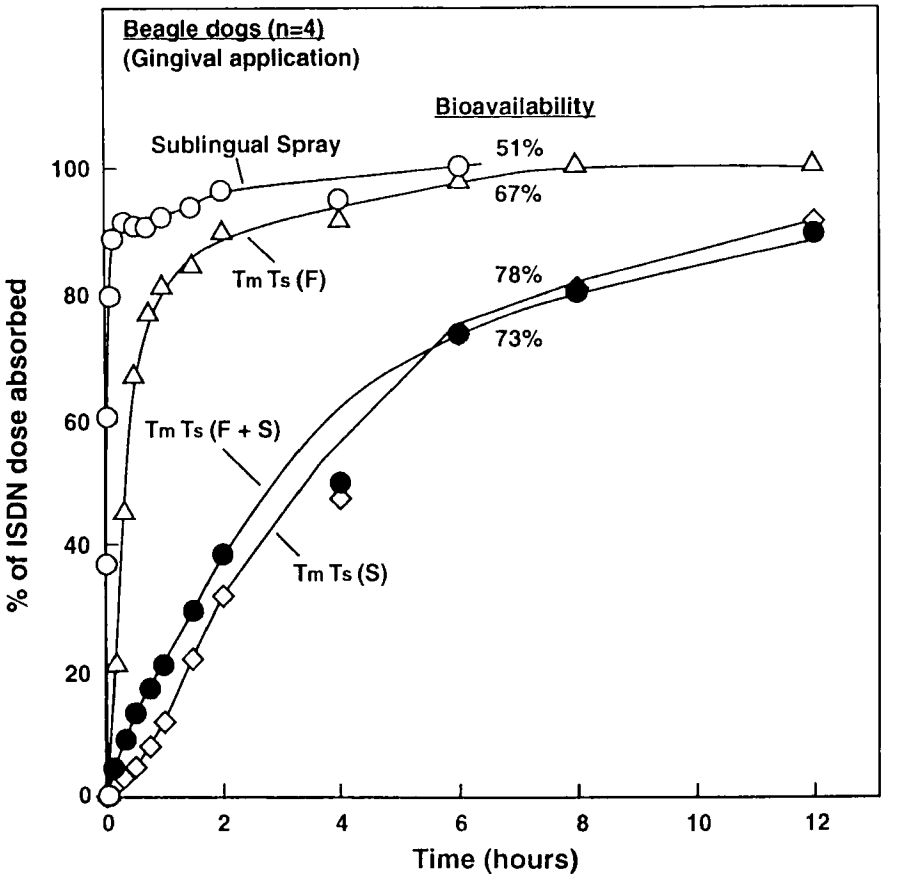

FIGURE 8
Effect of formulation on trans-mucosal absorption profiles and systemic bioavailability of ISDN in beagle dogs (n=4) Key : (○) sublingual spray (Nitrol® spray) , (△) fast-release formulation (F) , (◇) sustained-release formulation (S) , (●) full formulation (F+S)

comparison with that from a marketed spray formulation (Nitrol® spray). The relative contribution of ISDN released from the fast-release layer and sustained-release layer of the TmTs was also evaluated and the results indicated that the ISDN dose delivered by the fast-release layer contributes to the rapid absorption

of ISDN during the initial phase of transmucosal permeation, thus attaining the absorption profile simulating that from sublingual spray formulation, and the ISDN dose delivered gradually from the sustained-release layer has maintained the prolonged absorption profile of TmTs. A great systemic bioavailability of ISDN was achieved by TmTs than by sublingual spray (73 % vs. 51 %), which is the average of the bioavailabilities of ISDN from fast-release and sustained-release layers. The absorption profiles in Figure 8 substantiate the plasma profiles in Figure 7.

Both the plasma concentration profiles (Figure 7) and the cumulative absorption profiles (Figure 8) demonstrate that the fast-release layer contributes to the rapid absorption of ISDN and the sustained-release layer contributes to the prolonged duration of plasma concentration[13] as expected from the kinetic profile of dissolution (Figure 6). Thus, the TmTs of ISDN has the characteristics of prompt attainment of therapeutically effective plasma level by the rapid absorption of ISDN from the fast-release fraction and maintenance of a long duration of therapeutically-effective plasma level by the ISDN delivered at controlled rate from the sustained-release fraction. The absorption of ISDN from the oral mucosa is extremely rapid but the absorption of ISDN, following the spray administration, has

achieved a lower bioavailability of 51%. Thus, the results appear to suggest that the formulation with fast rate of release tends to achieve a lower level of bioavailability. The reason for achieving lower bioavailability from the fast rate of release could be attributed to the factor of swallowing.

Clinical Studies in Humans

1. Comparative Pharmacokinetics of ISDN in Healthy male volunteers following Oral Mucosa Absorption from TmTs vs. Sublingual Tablet

Figure 9 compares the plasma concentration profiles of ISDN following the gingival application of the TmTs (15mg of ISDN) with that following the sublingual administration of one conventional sublingual tablet (Nitrol®, 5mg) in healthy male volunteers[14]. A substantially-prolonged plasma profile of ISDN has been achieved by the TmTs, with MRT of 6.0(±0.3) hr, than by the sublingual tablet, with MRT of 1.2(±0.1) hr. Moreover, it is encouraging to observe that there is no statistical difference between the relative bioavailabilities of ISDN delivered by the TmTs and by Nitrol® after correcting the difference in the dose administered, suggesting that the systemic delivery of ISDN by the TmTs via transmucosal permeation through various

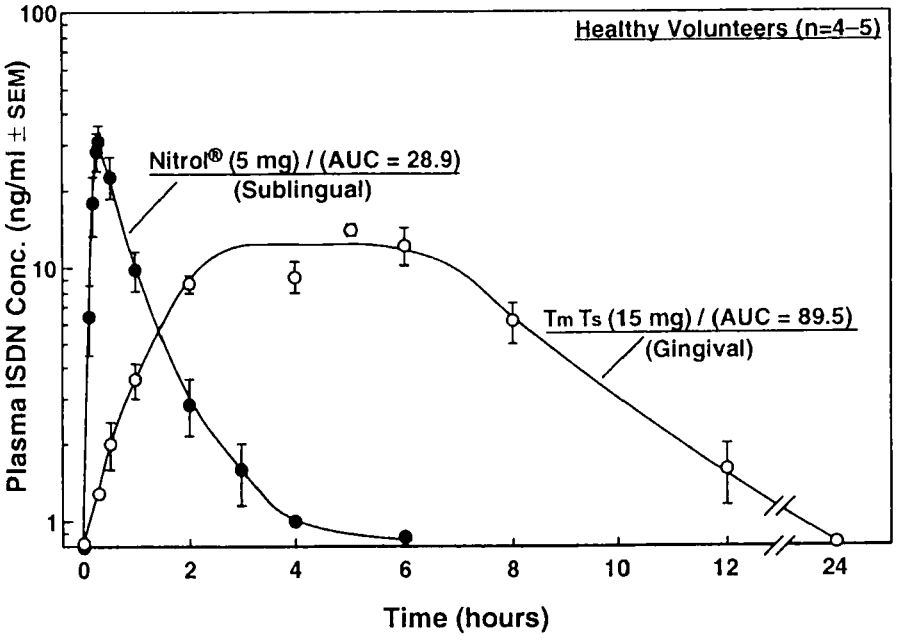

FIGURE 9
Comparative pharmacokinetic profiles of ISDN delivered trans-mucosally from : (○) a TmTs (15mg of ISDN) and (●) a sublingual tablet (Nitrol® , 5mg of ISDN) in healthy male volunteers (TmTs , n=5 ; Nitrol® , n=4)

oral mucosae is no difference from the sublingual absorption, since both are capable of bypassing the hepatic "first-pass" metabolism.

2. Bioavailability and Metabolism of ISDN in Healthy male volunteers following Oral Mucosa Absorption from TmTs vs. Oral Administration of Sustained-release Tablet

In Figure 10, the plasma concentration profiles of ISDN following the gingival application of the TmTs,

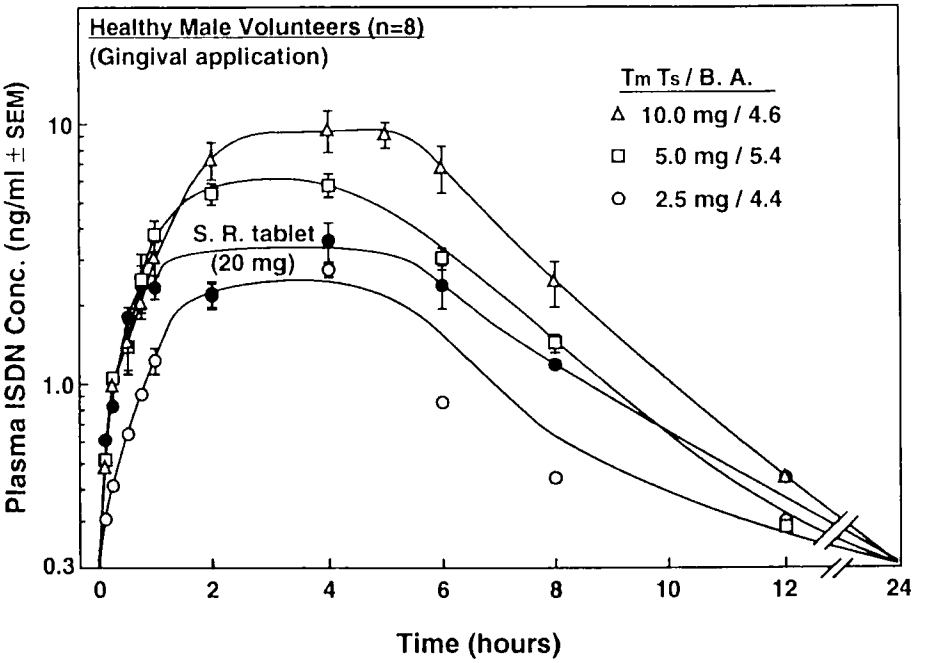

FIGURE 10
Comparative pharmacokinetic profile of ISDN delivered transmucosally from TmTs with varying loading dose and from a sustained-release tablet (S.R tablet , ●) taken orally in healthy male volunteers (n=8) , and 4-5 fold improvement in systemic bioavailability (B.A.)

with three dosage strengths, are compared with the plasma profile from the oral administration of a sustained-release oral tablet (Frandol® tablet; ISDN=20mg) in eight healthy male volunteers[14]. Both of the TmTs and the per-oral sustained-release tablet showed some similar sustained pattern in the plasma profile of ISDN. However, the plasma concentration profile of ISDN attained by the per-oral administration of sustained-

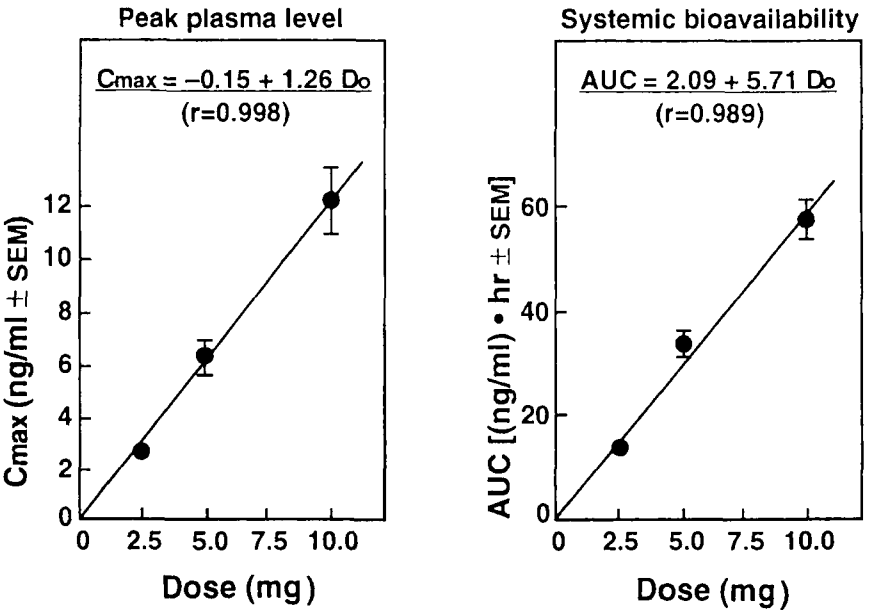

FIGURE 11
Linear relationship between Cmax and AUC following the trans-mucosal delivery of ISDN from TmTs in healthy male volunteers (n=8) and the loading dose in TmTs

release tablet, which contains 20mg of ISDN, were observed between those achieved by the TmTs containing only 2.5mg and 5mg of ISDN. Apparently, the systemic bioavailabilities achieved by the TmTs are 4.4-5.4 times greater than that obtained by the oral sustained-release tablet. Furthermore, a good linear relationship has been established between the Cmax values and the administered ISDN doses, and between the AUC values and the administered ISDN doses (Figure 11)[14].

As shown in Figure 2, ISDN is metabolized to two mononitrate metabolites, 2-ISMN and 5-ISMN, which are

also known to be pharmacologically active but have much lower antianginal efficacy than ISDN[15]. Thus, the hepatic "first-pass" metabolism leads to a reduction in the therapeutic efficacy of ISDN administered orally.

Contrast to the plasma concentration profiles of ISDN (Figure 10), the appearance of two metabolites, 2-ISMN and 5-ISMN, in the systemic circulation was found to be lower from the TmTs by transmucosal permeation than from the sustained-release tablet by the per-oral administration (Figure 12)[14]. Thus, the hepatic "first-pass" metabolism of ISDN has been efficiently minimized by the trans-mucosal permeation via the gingival application of the TmTs.

3. Pharmacokinetics after Repeated Administration

The plasma concentration profile of ISDN following the repeated gingival application of the TmTs (10mg of ISDN) to 6 healthy male volunteers, twice daily (9:00am and 9:00pm), for 7 days is shown in Figure 13[16]. The plasma concentration data measured experimentally were found to coincide rather well with the simulation curve generated from the one-compartment open pharmacokinetic model using the pharmacokinetic parameters[14] determined from the results of single administration (Figure 10)[14]. Figure 13 shows that the steady-state plasma

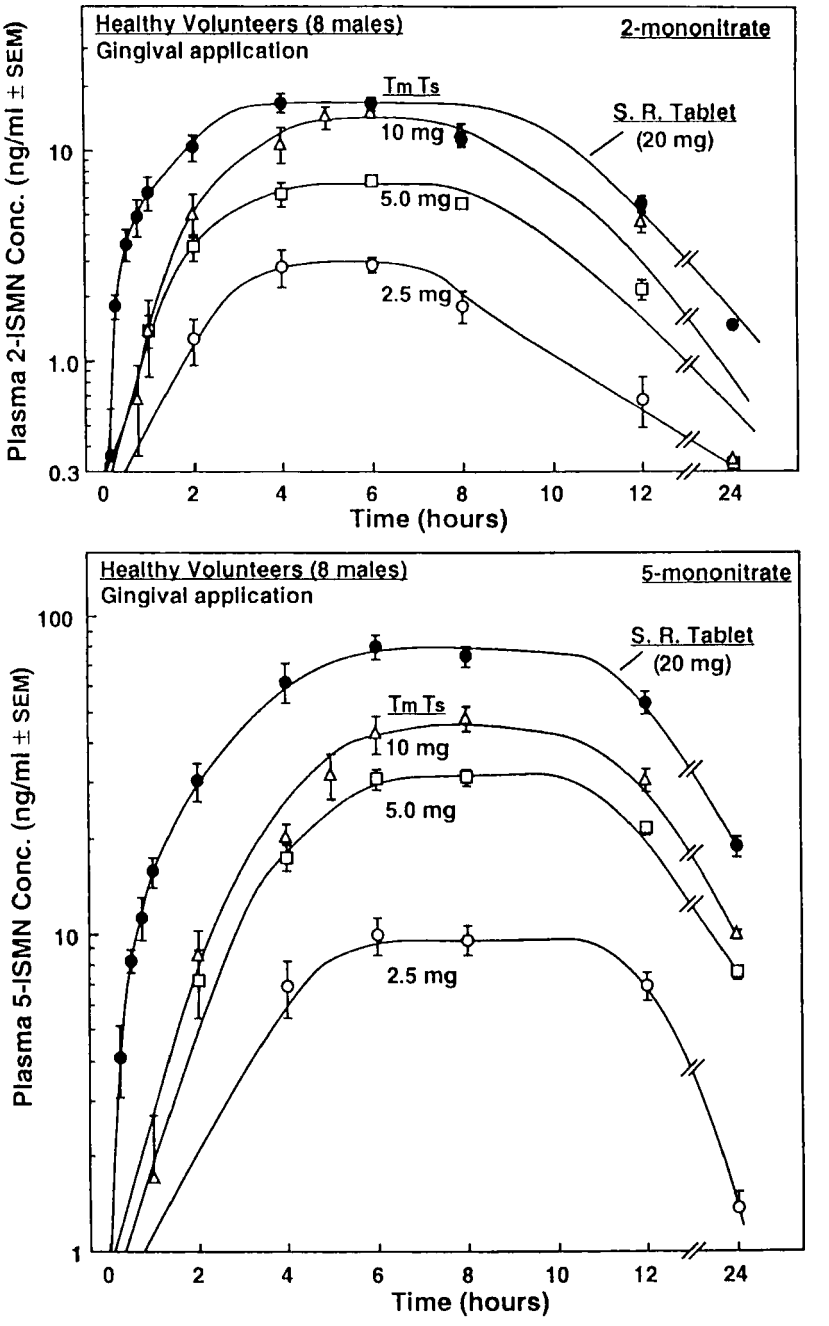

FIGURE 12
Comparative pharmacokinetic profiles of isosorbide mononitrates , the major metabolites , from TmTs (2.5-10.0mg) of ISDN and oral sustained-release tablet (Frandol® , 20mg ISDN) in healthy male volunteers (n=8)

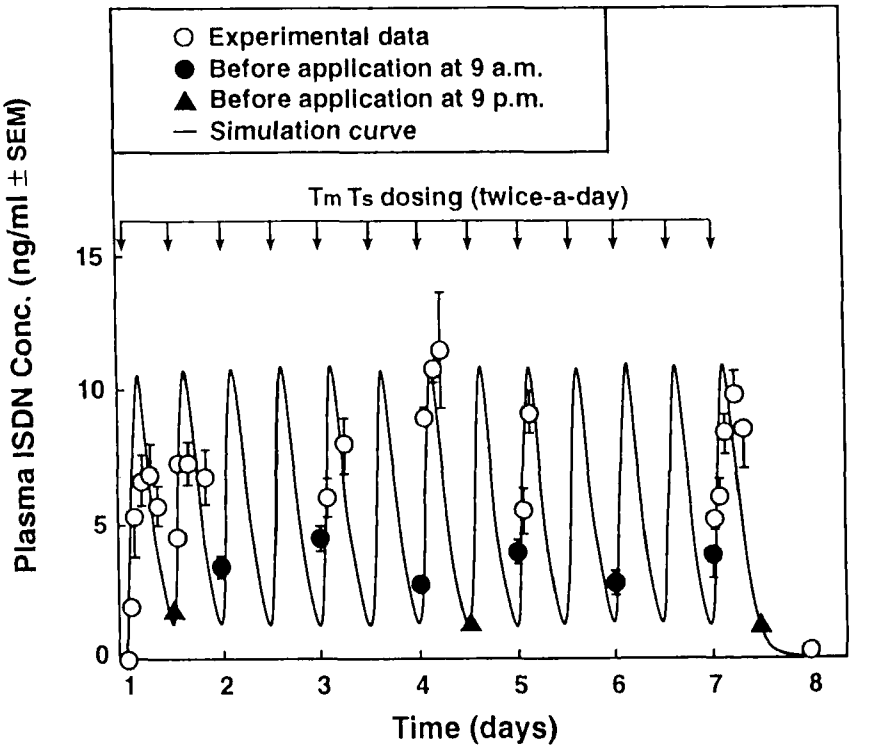

FIGURE 13
Multi-dose steady-state pharmacokinetic profile of ISDN following the repeated , twice daily , gingival application of TmTs (ISDN , 10mg) in healthy male volunteers (n=6) for 7days

profile of ISDN can be achieved and maintained by twice-a-day gingival application of TmTs, showing no tendency of accumulation of ISDN in the body. After administration of the last TmTs dose, ISDN is eliminated rapidly from the systemic circulation.

The cumulative urinary excretion profiles of ISDN and its metabolites are shown in Figure 14[16]. The relatively constant excretion of ISDN, which is extremely low, and the metabolites was confirmed.

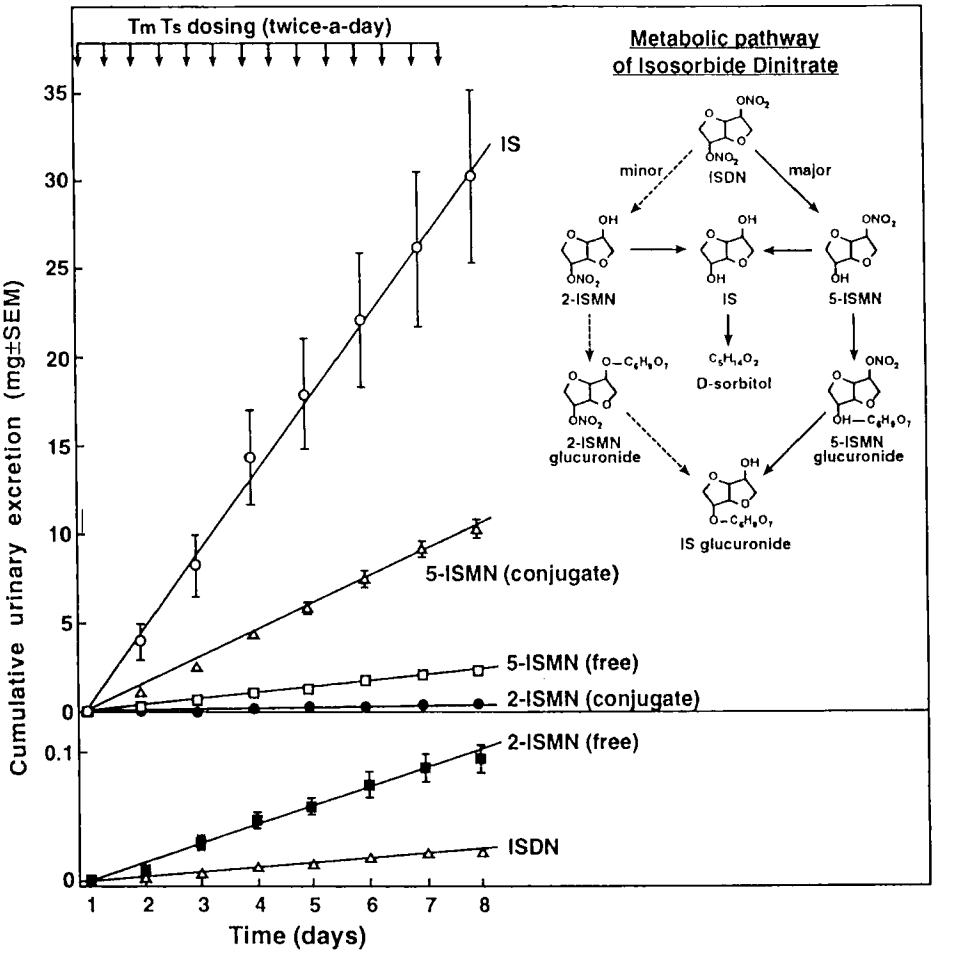

FIGURE 14
Urinary excretion profiles of ISDN and metabolites following continuous trans-mucosal delivery of ISDN during 7-day repeated, twice daily (9:00am , 9:00pm) , gingival application of TmTs (ISDN 10mg) in healthy male volunteers (n=6)

From these results, it is concluded that the pharmacokinetics of ISDN after repeated oral mucosa delivery of the TmTs is linear, and no accumulation has been observed as resulted from the saturation of absorption or excretion processes.

PHARMACODYNAMIC STUDIES in Anginal patients

Clinical Efficacy following Short-term Administration

In order to assess the therapeutic efficacy of ISDN delivered transmucosally from the TmTs having various pharmaceutic and pharmacokinetic characteristics outlined above, the effect of TmTs on the frequency of anginal attacks was first evaluated by short-term gingival application in 32 anginal patients. Among the 32 anginal patients, a total of 16 patients were omitted because they were found to be deviated from the criteria necessary for evaluating the clinical efficacy of angina pectoris. After a 2-week pretreatment period, during which the placebo TmTs was administered (also by gingival application, twice-a-day), the patients were administered with the active TmTs of 5mg in strength, at first, in the same manner for 2 weeks, and then the administration of active TmTs was continued for another 2 weeks with increased ISDN strength(10mg). The number of patients who had com-

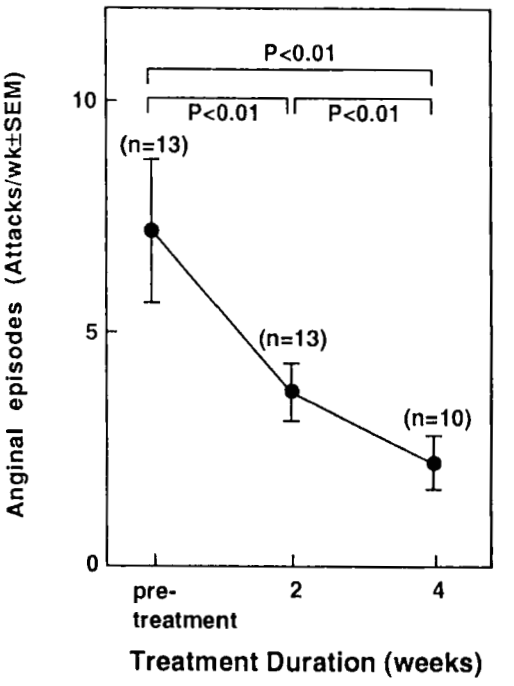

FIGURE 15
Statistically significant reduction in the frequency of anginal attacks in patients treated with TmTs (ISDN ; 5 or 10mg)

pleted the treatment was 13 in 5mg-treatment period and 10 in 10mg-treatment period, with some patients dropped out from the treatment due to side effect (e.g., headache), which is known to come from the pharmacological action of ISDN.

As shown in Figure 15, the results indicate that an average of anginal episodes/week has been decreased to 3.8 episodes/week by the 2-wk treatment with TmTs(5mg) and then to 2.3 episodes/week by the 2-wk

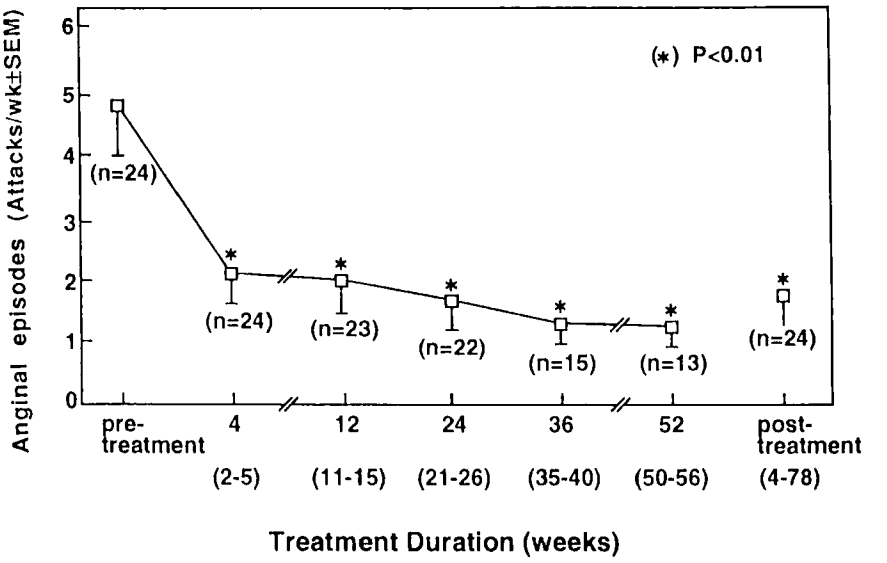

FIGURE 16
Long-term (1-yr) control of angina pectoris in patients by taking TmTs (5~20mg/day of ISDN)

treatment with TmTs(10mg) from the 7.2 episodes/week detected in the pretreatment period.

Thus, the clinical efficacy of the TmTs has been confirmed by the reduction in the frequency of anginal episodes measured in anginal patients.

Clinical Efficacy following Long-term Administration

The TmTs of ISDN was administered twice daily to 25 anginal patients by gingival application at 10 ~ 20 mg/day for an average duration of 46 weeks. The results shown in Figure 16 demonstrate that the anginal epi-

sodes in the 24 patients have been markedly decreased by treatment for 2-5 weeks, and a steady anti-anginal effect, with a mean episode of less than 2 attacks/wk, maintained throughout the treatment period. Thus, it is concluded that this system is useful also for long-term treatment of anginal patients.

APPLICATION OF TmTs TO NIFEDIPINE

To explore the potential application of TmTs in addition to ISDN, the transmucosal delivery of Nifedipine, which is also a well-known therapeutic agent for the treatment of anginal and hypertensive patients, was investigated. The formulation for Nifedipine was slightly modified from the TmTs of ISDN in order to attain a longer duration of action. By increasing the amount of polyvinylpyrrolidone of high molecular weight and polyacrylic acid in the sustained-release layer, the prolonged release of nifedipine for longer duration was achieved.

In Figure 17, the plasma profile of Nifedipine following the gingival application of the Nifedipine-releasing TmTs (20mg) is compared with those following the per-oral administration of a conventional oral tablet (Sepamit® ; Nifedipine=10mg) and a marketed sustained-release tablet (Adalat Retard® Nifedipine=20

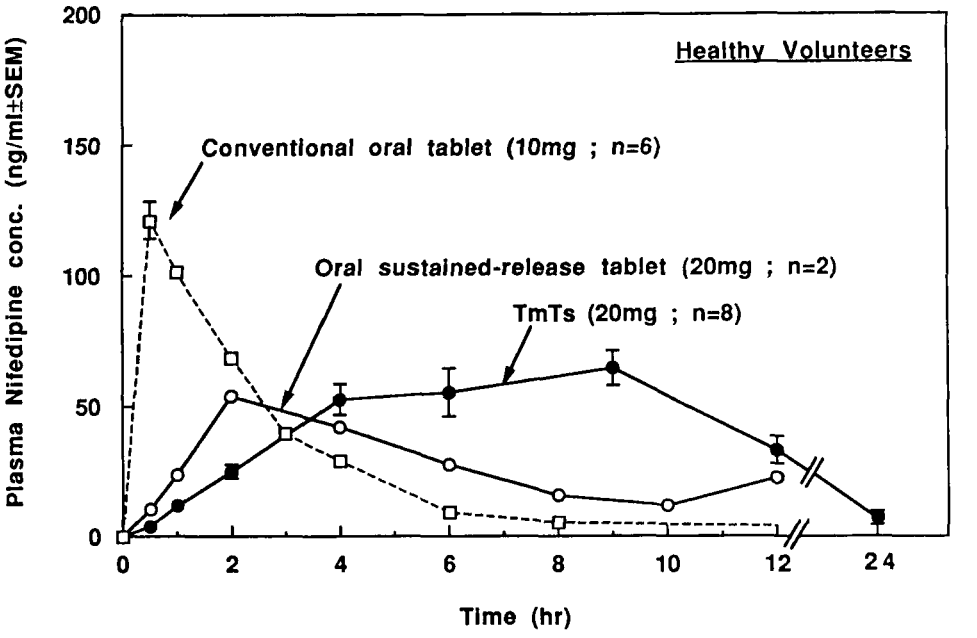

FIGURE 17
Comparative pharmacokinetic profiles of Nifedipine from TmTs in comparison with a conventional oral tablet (Sepamit®) and oral sustained-release tablet (Adalat retard®) in healthy male volunteers

mg) in healthy volunteers. The results indicate that a constant level of Nifedipine has been attained by 4/hrs and maintained throughout the period of 4-9 hr, which is much longer in duration than the conventional oral tablet and the marketed sustained-release tablet. The observations seem to promise a longer clinical efficacy of Nifedipine delivered by TmTs than that by the immediate-release or the sustained-release oral tablet.

CONCLUSION

Transmucosal permeation through oral mucosa permits the bypass of hepatic "first-pass" metabolism and has been considered to be a good site for the systemic delivery of drugs. Thus, many dosage forms have been designed to utilize the oral mucosa for drug delivery, such as lorenzes, trouches, sublingual tablets and oral ointments. However, these conventional dosage forms have their drawbacks for not being able to control drug release. Furthermore, patients have the tendency to swallow or crunch and cannot keep them in oral cavity for long period of time, and it is rather difficult to control the dose administered.

A new type of trans-mucosal therapeutic system (TmTs) which is designed for gingival application, has been developed. It has achieved a rapid and good adhesion to the gingival mucosa, caused neither irritation to the oral mucosae nor a sense of foreign material and produced a rapid rise but long duration of plasma drug concentration. The system is easy for manufacturing and composed of two layers : the upper one is a fast-release layer and the lower one is a sustained-release layer.

ISDN was selected as a candidate drug for assessing the potential biomedical application of this

system, since its therapeutic efficacy is well established but it is also known to be subjected to an extensive hepatic "first-pass" metabolism. The TmTs of ISDN was confirmed to achieve a desired pharmacokinetical profiles, such as a rapid attainment of therapeutic level and maintenance of prolonged plasma profile, in both beagle dogs and humans with achievement of better bioavailability of ISDN than the conventional dosage forms. By by-passing the hepatic "first-pass" metabolism of ISDN, the TmTs produced an almost 5 fold increase in the systemic bioavailability of ISDN in human as compared with that of a marketed oral sustained-release tablet. On the other hand, much lower levels of metabolites were obtained. The long-term gingival application, twice daily for one week, of the TmTs demonstrated that the steady-state plasma level of ISDN can be maintained with no sign of accumulation. In order to assess the therapeutic efficacy of the TmTs of ISDN, the frequency of anginal attacks in the anginal patients, following both short-term and long-term treatment, was measured and the results has demonstrated a remarkable reduction in anginal episodes.

The potential application of the system to other drugs was evaluated. The TmTs of Nifedipine was formulated by slightly modified from that of ISDN and the

results demonstrated that a much constant level of Nifedipine has been achieved and maintained for longer duration than the conventional or the sustained-release oral tablet.

Thus, it is believed that the trans-mucosal therapeutic system described in this presentation can be also applied to the trans-mucosal controlled systemic delivery of drugs in other therapeutic categories.

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